UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,673	03/23/2005	Tatsuo Hoshino	K21409USWO C038435/018565	2412

7590 08/11/2006

EXAMINER
RAGHU, GANAPATHIRAM

ART UNIT	PAPER NUMBER
1652	

Stephen M Haracz
Bryan Cave
1290 Avenue of the Americas
New York, NY 10104

DATE MAILED: 08/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/528,673	HOSHINO ET AL.	
	Examiner	Art Unit	
	Ganapathirama Raghu	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5-8,13 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/23/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *SEQ ALIGN*.

DETAILED ACTION

Claims 1-18 are pending in this application for examination. Claims 1, 2, 5-8, 13 and 16 are now under consideration. Claims 3-4, 9-12, 14-15 and 17-18 are withdrawn as they are drawn to non-elected invention.

Election/Restrictions

Applicant's election of Group I, claims 1, 2, 5-8, 13 and 16 with traverse for prosecution in the reply filed on July 16, 2006 is acknowledged. The traversal is on the grounds that the restriction is improper, unity of invention and a special technical feature exists between the restricted groups and all the claims are closely related and examination of all the claims will not pose a serious search burden.

Applicants' arguments of "No lack of unity was found by the Examiner and thus the restriction should be withdrawn" is answered as follows.

1.The traversal is on the grounds that the Office has not provided sufficient reasons for restriction of different groups and therefore restriction between groups should be withdrawn and have requested for examination of all the claims. Applicant's arguments have been fully considered but are not deemed persuasive to withdraw the restriction requirement previously applied. If the examiner finds that the national stage application lacks unity of invention under 37 CFR 1.475, the examiner may in an Office Action require the applicant in the response to that action to elect an invention to which the claims shall be restricted. Such requirement may be made before any action at the discretion of the examiner.

2. Applicant's argument of all the claims are linked by special technical features and have unity of invention is not persuasive because, Asakura et al., (EPO 832974 A2, date of publication 01/04/1998) teach the isolation of a polypeptide that is functionally annotated as alcohol/aldehyde dehydrogenase with 100% homology to the polypeptide with SEQ ID NO: 2 of the instant application. Said reference also teaches L-idose and L-idonic acid as substrates for the isolated polypeptide and said substrates are also included in the group of substrates used in the instant application for the synthesis of L-ascorbic acid. Therefore the technical features linking the inventions of Groups I-III does not constitute a special technical feature as defined by PCT Rule 13.2, as it does not define a contribution over the prior art, as the polypeptide with SEQ ID NO: 2 is the enzyme used in the reactions to synthesize L-ascorbic acid or the intermediates of L-ascorbic acid in groups I-III. Further evidence that the claims lack special technical feature is found under U.S.C. 102 (b) and U.S.C. 103 below.

Therefore contrary to applicant's argument, the requirement for restriction is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 23 March 2005 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the Examiner is considering the information disclosure statement.

Drawings

Drawings are accepted for examination purposes only.

Claim Rejections: 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and claims 6-7 depending therefrom; claim 2 and claims 5, 13 and 16 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 2 recite the phrase "...90% identical..., the metes and bounds of the phrase is not clear and the examiner suggests amending the phrase to "...with 90% sequence identity...". Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-2, 5-7, 13 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has the amino acid sequence of SEQ ID NO: 2 with the activity to produce L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with the said enzyme, does not reasonably provide enablement for the

production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has an amino acid sequence 90% identical to SEQ ID NO: 2 or thereto from any source including variants, mutants and recombinants, with the activity to produce L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with the claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-2, 5-7, 13 and 16 are so broad as to encompass the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has an amino acid sequence 90% identical to SEQ ID NO: 2 or thereto from any source including variants, mutants and recombinants, with the activity to produce L-ascorbic acid under specific defined process conditions such as pH, temperature and

time in which the substrates are allowed to react with said enzyme. The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. Since the amino acid sequence of a protein encoded by a polynucleotide determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires knowledge and guidance with regard to which amino acids in the protein's sequence and the respective codons in its polynucleotide, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the encoded proteins' structure relates to its function. However, in this case the disclosure is limited to production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, Lgalactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has the amino acid sequence of SEQ ID NO: 2 with the activity to produce L-ascorbic acid under the prescribed conditions of pH, temperature and time for the process. The specification is limited to teaching the use of an enzyme having the amino acid sequence of SEQ ID NO: 2 with the activity to produce L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme, but provides no guidance with regard to the making of other variants, mutants and recombinants from any source or with regard to other uses. In view of the great breadth of the claims, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary

structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by these claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is not routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions or deletions.

The specification does not support the broad scope of the claims which encompass the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has an amino acid sequence 90% identical to SEQ ID NO: 2 or thereto from any source including variants, mutants and recombinants, with the activity to produce L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme, because the specification does not establish: (A) regions of SEQ ID NO: 2 protein/polynucleotide structure that can be modified without affecting the activity to produce L-ascorbic acid under specific

defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme; (B) the general tolerance of the polypeptide with SEQ ID NO: 2 and the encoding polynucleotide to modification and extent of such tolerance; (C) a rational and predictable scheme for modification with any amino acid residue or the respective codon in the encoding polynucleotide with an expectation of obtaining the desired biological function i.e., the activity to produce L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polypeptides with an enormous number of modifications for a process of producing L-ascorbic acid. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5-8, 13 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Asakura et al., (EPO 832974 A2, date of publication 01/04/1998) when given the broadest interpretation. Claims 1, 2, 5-8, 13 and 16 are directed to a process for the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of, L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence 90% identical to SEQ ID NO: 2 thereto, with the activity to produce L-ascorbic acid (claims 1-2) and to a process for producing L-ascorbic acid comprising contacting a substrate which is selected from L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid with Enzyme B of *G.oxydans* DSM 4025 and isolating L-ascorbic acid from the reaction, wherein Enzyme B has the following physico-chemical properties: a) molecular weight of about 60, 000 Da on SDS-PAGE; b) substrate specificity for primary and secondary alcohols and aldehydes; c) pH stability at a pH of about 6 to about 9; d) pH optimum of about 8.0; and e) inhibited by Cu^{2+}, Zn^{2+}, Mn^{2+}, $Fe^{2+}$and Fe^{3+} under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme (claims 5-8, 13 and 16).

Asakura et al., (*supra)* disclose the purification, kinetic profiles and physico-chemical characterization of a polypeptide designated as Enzyme B from *G.oxydans* DSM 4025 that has 100% sequence homology to SEQ ID NO: 2 of the instant application with identical physico-

chemical properties and substrate specificity for primary and secondary alcohols, optimal pH range, pH stability, thermal stability and effect of metals and inhibitors on the activity of said enzyme (Table: 1, 2, 3, 4 and 5). Furthermore, Table 10, page 23 discloses L-idose as a substrate for Enzyme B and the formation of L-idonic acid and the use of said enzyme in a process for the production of L-ascorbic acid and the intermediates of L-ascorbic acid (Abstract section). Therefore the reference of Asakura et al., anticipates the claims 1, 2, 5-8, 13 and 16 as written.

Claim Rejections: 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 5-8, 13 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Asakura et al., (EPO 832974 A2, date of publication 01/04/1998) and further in view of Bourdant et al., (Enzyme Micro. Technol., 1990, Vol. 12, pages 322-329) and Hancock et al., (TRENDS in Biotechnol., 2002, Vol. 20 No. 7, pages 299-305). Claims 1-2, 5-8, 13 and 16 are directed to a process for the production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid, wherein said enzyme has the amino acid sequence of SEQ ID NO: 2 or an amino acid sequence 90% identical to SEQ ID NO: 2 thereto, with the activity to produce L-ascorbic acid under specific defined process conditions such as pH, temperature and time in which the substrates are allowed to react with said enzyme.

Asakura et al., (*supra*) teach the purification, kinetic profiles and physico-chemical characterization of a polypeptide designated as Enzyme B from *G.oxydans* DSM 4025 that has 100% sequence homology to SEQ ID NO: 2 of the instant application with identical physico-chemical properties and substrate specificity (as discussed in 102 (b)) rejection above). However, said reference is silent regarding the some of the substrates selected from the group L-gulose, L-galactose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-talono-1,4-lactone and L-talonic acid.

Bourdant et al., and Hancock et al., (*supra*) teach the different processes and conditions for the production of L-ascorbic acid, such as The Reichstein process, Bacterial fermentation processes and the different pathways, substrates and products such as L-sorbose, L-gulonic acid,

L-idonic acid to 2,keto-L-gulonic acid or 2,keto-L-idonic acid utilized by bacteria and the enzymes produced by the bacteria in the production of L-ascorbic acid (entire document).

The instant application relates to a process of production of L-ascorbic acid comprising: contacting an enzyme with a substrate selected from the group consisting of, L-gulose, L-galactose, L-idose, L-talose, L-gulono-1,4-lactone, L-gulonic acid, L-galactono-1,4-lactone, L-galactonic acid, L-idono-1,4-lactone, L-idonic acid, L-talono-1,4-lactone and L-talonic acid .

Combining the teachings of the above references, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to develop a process for the production of L-ascorbic acid using the enzyme taught by Asakura et al., wherein they disclose the different substrates and intermediate products made by Enzyme B from *G.oxydans* DSM 4025 including the substrate L-idose and intermediate product L-idonic acid and further suggest enzyme's use in L-ascorbic acid synthesis. One of ordinary skill in the art would have been motivated to make or use such an enzyme in the production of L-ascorbic acid and one of ordinary skill in the art would have had a reasonable expectation of success, since the references of Bourdant et al., and Hancock et al., (*supra*) teach the various pathways and a list of intermediates and substrates that can be employed for the production of L-ascorbic acid, further strengthening the motivation and reasonable expectation of success to use Enzyme B of *G.oxydans* DSM 4025 with the substrates disclosed in the present invention for the production of L-ascorbic acid.

Therefore, the above references render claims 1, 2, 5-8, 13 and 16 *prima facie* obvious to one of ordinary skill in the art.

Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on 8 am - 5 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.
Patent Examiner
Art Unit 1652

July 28, 2006.